

Structure–Activity Relationships of 1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)pyrimidine Nucleosides as Anti-Hepatitis B Virus Agents

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Since 2'-fluoro-5-methyl- β -L-arabinofuranosyluracil (L-FMAU) has been shown to be a potent anti-HBV agent *in vitro*, it was of interest to study the structure–activity relationships of related nucleosides. Thus, a series of 1-(2-deoxy-2-fluoro- β -L-arabinofuranosyl)pyrimidine nucleosides have been synthesized and evaluated for antiviral activity against HBV in 2.2.15 cells. For this study, L-ribose was initially used as the starting material. Due to the commercial cost of L-ribose, we have developed an efficient procedure for the preparation of L-ribose derivative **6**. Starting from L-xylose, **6** was obtained in an excellent total yield (70%) through the pyridinium dichromate oxidation of the 3-OH group followed by stereoselective reduction with NaBH₄. It was further converted to the 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro- α -L-arabinofuranose (**10**), which was then condensed with various 5-substituted pyrimidine bases to give the nucleosides. Among the compounds synthesized, the lead compound, L-FMAU (**13**), exhibited the most potent anti-HBV activity (EC₅₀ 0.1 μ M). None of the other uracil derivatives showed significant anti-HBV activity up to 10 μ M. Among the cytosine analogues, the cytosine (**27**) and 5-iodocytosine (**35**) derivatives showed moderately potent anti-HBV activity (EC₅₀ 1.4 and 5 μ M, respectively). The cytotoxicity of these nucleoside analogues has also been assessed in 2.2.15 cells as well as CEM cells. None of these compounds displayed any toxicity up to 200 μ M in 2.2.15 cells. Thus, compound **13** (L-FMAU), **27**, and **35** showed a selectivity of over 2000, 140, and 40, respectively.

Introduction

Recently, a number of nucleosides with the unnatural L-configuration have been reported as potent chemotherapeutic agents against human immunodeficiency virus (HIV), hepatitis B virus (HBV), and certain forms of cancer. These include (–)- β -L-1-[2-(hydroxymethyl)-1,3-oxathiolan-4-yl]cytosine (3TC),^{1–3} (–)- β -L-1-[2-(hydroxymethyl)-1,3-oxathiolan-4-yl]-5-fluorocytosine (FTC),^{4,5} (–)- β -L-2', 3'-dideoxypentofuranosyl-5-fluorocytosine (L-FddC),^{6,7} and (–)- β -L-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]cytosine [(–)-OddC].^{8,9} It is interesting that these L-nucleosides have potent biological activity, while some of them show lower toxicity profiles than their D-counterparts. In view of this interesting discovery of L-nucleosides as biologically active compounds, we have recently synthesized 2'-fluoro-5-methyl- β -L-arabinofuranosyluracil (L-FMAU) and its derivative and evaluated these compounds as potential antiviral agents. From this effort we discovered L-FMAU as a potent antiviral agent against HBV as well as the Epstein–Barr virus.¹⁰ In contrast to the D-enantiomers, L-FMAU did not exhibit any toxicities, including the interference of mitochondrial function,¹¹ resulting in lactic acidosis and hepatic failure as shown by β -D-2'-fluoro-5-iodoarabinofuranosyluracil (Fialuridine, D-FIAU).¹² No significant bone marrow toxicity was found for L-FMAU up to 100 μ M.¹⁰ Furthermore, in preliminary *in vivo* toxicity studies in mice for 30 days, L-FMAU did not show any apparent toxicities as well as significant abnormalities of clinical chemistry.¹³ Additionally, L-FMAU exhibited *in vivo* antiviral activity against the duck hepatitis B

virus in the Peking duck hepatitis model.¹⁴ We also studied the biochemical mode of action of L-FMAU, in which it was discovered that L-FMAU is phosphorylated by the cellular thymidine kinase as well as by deoxycytidine kinase to the monophosphate and subsequently to the triphosphate by unknown kinases, which inhibits the HBV DNA polymerase.¹⁵ However, we failed to detect any incorporation of a radiolabeled nucleoside to either the HBV DNA or the cellular DNA. Furthermore, the triphosphate did not inhibit cellular DNA polymerases.¹⁵ As a result of these promising pharmacological and toxicological profiles, L-FMAU is currently considered as a clinical candidate for treatment of chronic HBV infection. In view of these promising results obtained for L-FMAU, it was of interest to study the structure–activity relationships (SAR) of the related class of nucleosides. Therefore, in this paper we report the synthesis and the SARs of 1-(2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-substituted-pyrimidine nucleosides as potential anti-HBV agents.

Results and Discussion

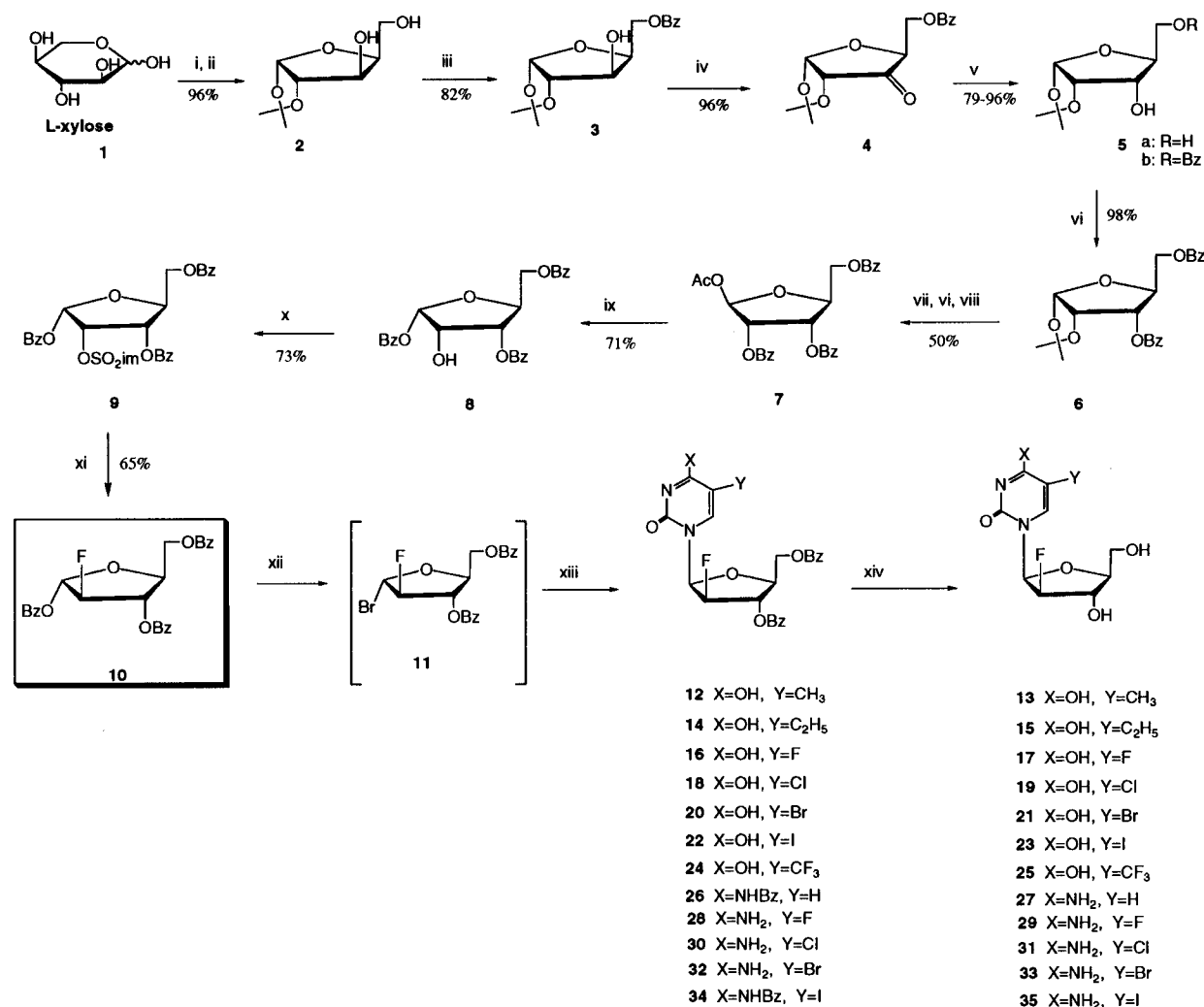
Synthesis. The synthesis of 2'-deoxy-2'-fluoro- β -L-arabinofuranosyl nucleosides reported in this paper was accomplished *via* the key intermediate **10**, which was initially prepared¹⁰ from L-ribose according to a similar procedure used for the synthesis of D-FMAU.¹⁶ However, due to the high commercial cost of L-ribose as a starting material, we developed a synthetic procedure for the L-ribose derivative **6**. Although several procedures have been reported for the synthesis of L-ribose,^{17–20} on the basis of our experience, none of these methods seemed practical for large-scale preparation. Previously, it was reported that D-ribose was

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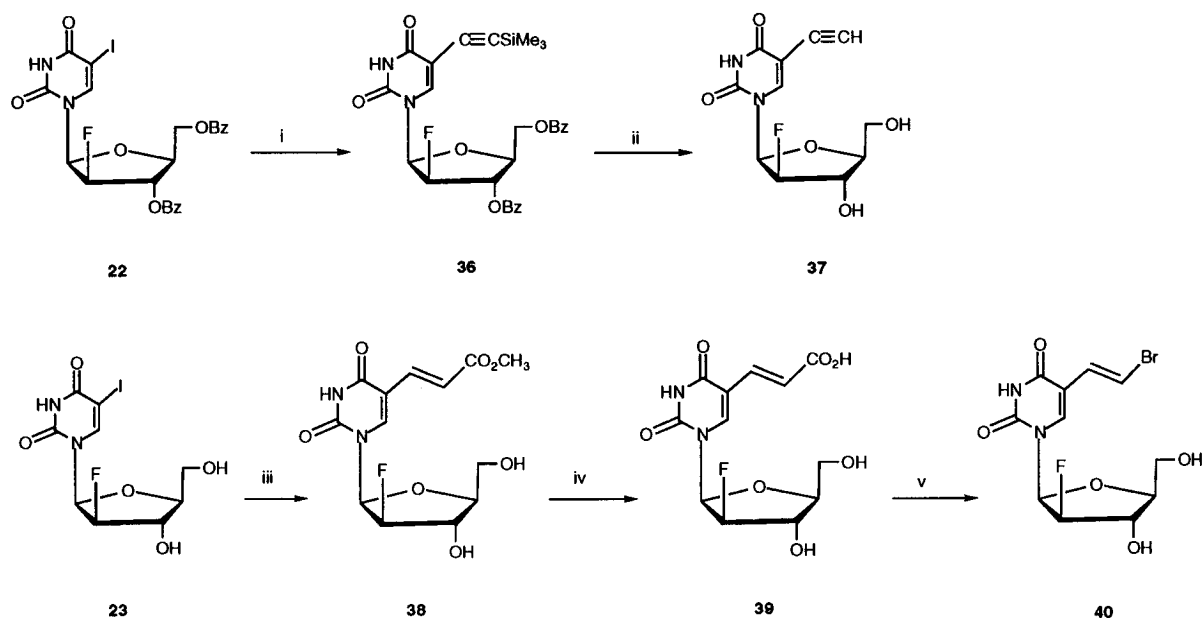
Scheme 1^a

^a Reagents: (i) CuSO₄, concentrated H₂SO₄, acetone; (ii) 0.2% HCl/H₂O; (iii) BzCl, py, CH₂Cl₂, 0 °C, 0.5–1 h; (iv) PDC, Ac₂O, CH₂Cl₂, reflux; (v) NaBH₄, 80% EtOH/H₂O or NaBH₄, EtOH, EtOAc; (vi) BzCl, py; (vii) 1% HCl/CH₃OH; (viii) Ac₂O, AcOH, concentrated H₂SO₄; (ix) (1) HCl(g), AcCl, CH₂Cl₂, 0 °C, (2) H₂O, CH₃CN; (x) SO₂Cl₂, DMF, CH₂Cl₂, –15 °C to room temperature, imidazole; (xi) KHF₂, 2,3-butanediol, 48% HF/H₂O, reflux; (xii) HBr/AcOH, CH₂Cl₂, room temperature; (xiii) silylated bases, 1,2-dichloroethane, reflux; (xiv) NH₃/CH₃OH.

synthesized from D-xylose *via* the oxidation–reduction procedure of the 3-OH group, albeit in a low yield.²¹ We decided to adopt this strategy to synthesize the L-ribose derivative (Scheme 1). Thus, 1,2-*O*-isopropylidene-α-L-xylofuranose (**2**) was prepared from L-xylose,²² which was then selectively protected at the 5-OH with BzCl in pyridine–CH₂Cl₂ at 0 °C to give **3** (79% yield from **1**). Although various oxidizing agents have been reported for the oxidation of the 3-OH of pentofuranose derivatives,^{21,23,24} we found pyridinium dichromate (PDC) gave the best yield (96%). The resulting ketone **4** was stereoselectively reduced by NaBH₄ to the desired ribose derivative **5**. It should be mentioned that apparently due to the stereoelectronic effects of the 1,2-*O*-isopropylidene group, the hydride only attacked from the β-face, resulting in 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-L-ribofuranose (**5b**) as the exclusive product. When EtOH–H₂O (4:1) was used as the solvent, cleavage of the benzoyl group occurred, leading to a cumbersome workup and a lower yield (79%); however, using a mixture of EtOAc–EtOH (1:2) prevented the cleavage of the benzoyl group, resulting in a higher yield (96%). Compound **5a** or **5b** was benzoylated to give the dibenzoylated ribose derivative **6**,²⁵ which was treated suc-

cessively without isolation with 1% HCl–MeOH, BzCl–pyridine, and then Ac₂O–AcOH–H₂SO₄ to give 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (**7**) as a crystalline product in 50% yield. Treatment of **7** with saturated hydrogen chloride in CH₂Cl₂ at 0 °C followed by hydrolysis²⁶ gave **8** (71% yield), which was treated with SO₂Cl₂ and imidazole in DMF–CH₂Cl₂ to give the imidazolyl sulfonate **9** in 73% yield. The imidazole derivative **9** was fluorinated with KHF₂ and 48% HF–H₂O to give 1,3,5-tri-*O*-benzoyl-2-fluoro-α-L-arabinofuranose (**10**) in 65% yield.¹⁶ It is noteworthy to mention that an improved fluorination reaction was recently reported.²⁷

Bromination of the key intermediate **10** with HBr–AcOH gave a bromo derivative **11**, which was coupled with silylated thymine without catalyst in CH₃CN under refluxing conditions to give the protected nucleoside **12** as a mixture of anomers (β:α/3:1). Although the reaction finished within 3 h and the yield was high (94%), the separation of the anomers was difficult in both the protected as well as deprotected stages. Therefore, we searched for a more convenient procedure to improve the β/α ratio. From these efforts we found that using 1,2-dichloroethane (DCE) as the solvent for the conden-

Scheme 2^a

^a Reagents: (i) Et₃N, (Ph₃P)₂PdCl₂, CuI, (trimethylsilyl)acetylene, Ar, 50 °C; (ii) NaOCH₃, CH₃OH; (iii) methyl acrylate, Pd(OAc)₂, Ph₃P, 1,4-dioxane; (iv) (1) NaOH, (2) HCl; (v) DMF, KHCO₃, *N*-bromosuccinimide.

sation gave mainly the β -isomer **12** along with only trace amount of the α -anomer, which was easily removed by silica gel column chromatography or recrystallization, although the coupling reaction took a longer time with a lower yield (71%). We also found that using CHCl₃ as the solvent for the coupling reaction gave the best β/α ratio (20/1) which was consistent with the previously reported result.²⁸ The bromo sugar **11** was also condensed with other silylated 5-substituted uracil derivatives to give the protected nucleosides (**14**, **16**, **18**, **20**, **22**, and **24**), which were treated with NH₃-CH₃OH to give the final products (**15**, **17**, **19**, **21**, **23**, and **25**). The synthesis of cytosine derivatives was achieved by the condensation of the bromo sugar **11** with either the *N*-benzoylated (**26** and **34**) or unprotected bases (**28**, **30**, and **32**) in 1,2-dichloroethane. No significant differences in yields of the condensation was observed. The free nucleosides (**27**, **29**, **31**, **33**, and **35**) were obtained by the deprotection of **26**, **28**, **30**, **32**, and **34** with NH₃-CH₃OH.

The 5-ethynyluracil derivative **37** was obtained by treatment of the protected 5-iodo derivative **22** with (trimethylsilyl)acetylene in the presence of (Ph₃P)₂PdCl₂ and CuI, followed by deprotection with NaOCH₃-CH₃-OH.²⁹ The synthesis of the (*E*)-5-bromovinyl derivative **40** was accomplished by using a similar procedure reported for the synthesis of 5-(bromovinyl)-2'-deoxyuridine (BVDU)³⁰ (Scheme 2). Thus, the free 5-iodouracil derivative **23** was treated with methyl acrylate in the presence of Pd(OAc)₂ and Ph₃P in dioxane. Saponification with NaOH followed by acidification with HCl gave **39**, which was decarboxylated in DMF in the presence of *N*-bromosuccinimide and K₂CO₃ to give **40**. The *E*-configuration was identified by the coupling constant (13.6 Hz) for the vinyl protons in the ¹H NMR spectrum.

The physical data for all the key intermediates and final products are summarized in Table 1. β -L-configuration of the synthesized nucleosides was confirmed by comparison of the ¹H NMR spectra (Table 2) with those of the corresponding D-isomers.^{16,31-34} The C_{1'}-F

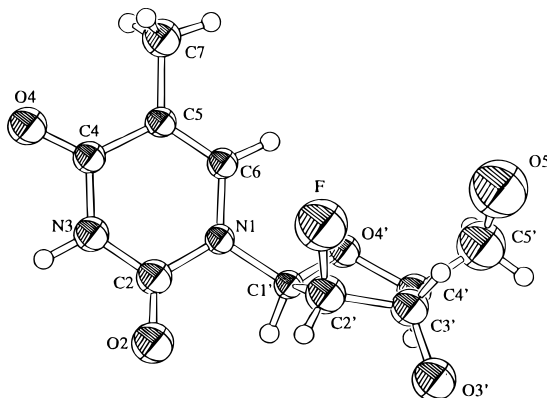


Figure 1. ORTEP drawing of L-FMAU.

coupling constants (16–18 Hz) in the ¹³C NMR spectra were consistent with those reported for the β -D-configuration.³⁵ The structure of β -L-FMAU was also unambiguously confirmed by a single-crystal X-ray crystallography,³⁶ and the ORTEP drawing is shown in Figure 1.

Anti-Hepatitis B Virus Activity. The anti-hepatitis B virus activity (EC₅₀) and growth inhibition (IC₅₀) of the synthesized nucleosides were evaluated in 2.2.15 cells as previously described¹⁰ and are shown in Table 3. Unlike the D-isomers such as FMAU, FEAU, and FIAU, neither 5-substitutions with halogen (F, Cl, Br, I) nor 5-substitutions with alkyl groups (ethyl, *E*-bromovinyl, or ethynyl) exhibited any significant anti-HBV activity up to 10 μ M. The only active uracil derivative is the 5-methyl derivative, L-FMAU (**13**), which exhibited 20 times more potency than that of the D-counterpart (EC₅₀ 0.1 μ M vs 2.0 μ M).¹⁰ Change of the 5-methyl to a 5-trifluoromethyl group (**25**) also resulted in a decrease of the anti-HBV activity. Interestingly, the cytosine (**27**) and 5-iodocytosine (**35**) derivatives showed moderately potent anti-HBV activities (EC₅₀ 1.4 and 5.0 μ M, respectively), while other 5-substitutions such as F, Cl, and Br did not exhibit any significant antiviral activity.

Table 1. Physical and Optical Data

no.	mp, °C (solvent) ^a	[α] ²⁵ _D	formula	anal.
3	82–83 (A)	–12.14 (<i>c</i> 0.37, CHCl ₃)	C ₁₅ H ₁₈ O ₆	C, H
4	91–93 (B)	–132.00 (<i>c</i> 1.0, CHCl ₃)	C ₁₅ H ₁₆ O ₆	C, H
5a	86–87 (B)	–31.50 (<i>c</i> 0.62, CHCl ₃)	C ₈ H ₁₄ O ₅	C, H
5b	131–132 (B)	+46.22 (0.11, CH ₃ OH)	C ₁₅ H ₁₈ O ₆	C, H
6	83–85 (A)	–122.38 (<i>c</i> 0.9, CHCl ₃)	C ₂₂ H ₂₂ O ₇	C, H
8	137–138 (A)	–81.96 (<i>c</i> 0.55, CHCl ₃)	C ₂₆ H ₂₂ O ₈ ·0.3H ₂ O	C, H
9	124–125 (B)	–68.98 (<i>c</i> 0.37, CHCl ₃)	C ₂₉ H ₂₄ N ₂ O ₁₀ S	C, H, N, S
10	77–78 (D)	–4.82 (<i>c</i> 0.51, CHCl ₃)	C ₂₆ H ₂₁ FO ₇ ·0.5C ₂ H ₅ OH	C, H, F
12	118–120 (E)	+22.40 (<i>c</i> 0.31, CHCl ₃)	C ₂₄ H ₂₁ FN ₂ O ₇ ·0.5CH ₃ OH	C, H, F, N
13	184–185 (E)	–111.77 (<i>c</i> 0.23, CH ₃ OH)	C ₁₀ H ₁₃ FN ₂ O ₅ ·0.2H ₂ O	C, H, F, N
14	148–149 (E)	+23.62 (<i>c</i> 0.21, CHCl ₃)	C ₂₅ H ₂₃ FN ₂ O ₇	C, H, F, N
15	158–161 (E)	–96.30 (<i>c</i> 0.47, CH ₃ OH)	C ₁₁ H ₁₅ FN ₂ O ₅	C, H, F, N
16	190–193 dec (E)	+10.76 (<i>c</i> 0.29, CHCl ₃)	C ₂₃ H ₁₈ F ₂ N ₂ O ₇ ·0.5H ₂ O	C, H, N
17	167–168 (E)	–93.42 (<i>c</i> 0.29, CH ₃ OH)	C ₉ H ₁₀ F ₂ N ₂ O ₅ ·0.2H ₂ O	C, H, N
18	189–191 (E)	+30.45 (<i>c</i> 0.35, CHCl ₃)	C ₂₃ H ₁₈ ClFN ₂ O ₇	C, H, N
19	195–196 (F)	–107.23 (<i>c</i> 0.18, CH ₃ OH)	C ₉ H ₁₀ ClFN ₂ O ₅ ·0.33C ₂ H ₅ OH	C, H, N
20	193–195 (E)	+37.65 (<i>c</i> 0.28, CHCl ₃)	C ₂₃ H ₁₈ BrFN ₂ O ₇ ·0.5CHCl ₃	C, H, N
21	214–215 (F)	–109.61 (<i>c</i> 0.15, CH ₃ OH)	C ₉ H ₁₀ BrFN ₂ O ₅ ·0.5C ₂ H ₅ OH	C, H, N
22	194–195 (G)	+44.02 (<i>c</i> 0.21, CHCl ₃)	C ₂₃ H ₁₈ FIN ₂ O ₇	C, H, F, I, N
23	218–220 (E)	–57.82 (<i>c</i> 0.33, CH ₃ OH)	C ₉ H ₁₀ FIN ₂ O ₅	C, H, F, I, N
24	186–187 (E)	+5.19 (<i>c</i> 0.21, CHCl ₃)	C ₂₄ H ₁₈ F ₄ N ₂ O ₇	C, H, N
25	202–203 (G)	–87.47 (<i>c</i> 0.33, CH ₃ OH)	C ₁₀ H ₁₀ F ₄ N ₂ O ₅	C, H, N
26	foam	–4.33 (<i>c</i> 0.21, CHCl ₃)	C ₃₀ H ₂₄ FN ₃ O ₇	C, H, N
27	240–242 (E)	–114.17 (<i>c</i> 0.21, CH ₃ OH)	C ₉ H ₁₂ FN ₃ O ₄ ·0.7H ₂ O·0.2CH ₃ OH	C, H, N
28	foam	–6.70 (<i>c</i> 0.35, CHCl ₃)	C ₂₃ H ₁₉ F ₂ N ₃ O ₆ ·0.5H ₂ O	C, H, N
29	188–189 dec (F)	–108.36 (<i>c</i> 0.16, CH ₃ OH)	C ₉ H ₁₁ F ₂ N ₃ O ₄	C, H, N
30	foam	+23.15 (<i>c</i> 0.19, CHCl ₃)	C ₂₃ H ₁₉ ClFN ₃ O ₆ ·0.6H ₂ O	C, H, N
31	205–206 (F)	–99.54 (<i>c</i> 0.26, CH ₃ OH)	C ₉ H ₁₁ ClFN ₃ O ₄ ·0.5C ₂ H ₅ OH	C, H, N
32	foam	+24.09 (<i>c</i> 0.27, CHCl ₃)	C ₂₃ H ₁₉ BrFN ₃ O ₆	C, H, N
33	201–202 (F)	–82.86 (<i>c</i> 0.18, CH ₃ OH)	C ₉ H ₁₁ BrFN ₃ O ₄ ·0.2C ₂ H ₅ OH	C, H, N
34	226–228 (E)	+41.29 (<i>c</i> 0.19, CHCl ₃)	C ₃₀ H ₂₃ FIN ₃ O ₇	C, H, F, I, N
35	211–212 dec (E)	–65.40 (<i>c</i> 0.34, CH ₃ OH)	C ₉ H ₁₁ FIN ₃ O ₄	C, H, F, I, N
36	212–214 (E)	+80.63 (<i>c</i> 0.19, CHCl ₃)	C ₂₈ H ₂₇ FN ₂ O ₇ Si·0.5H ₂ O	C, H, N
37	206–208 dec (H)	–89.52 (<i>c</i> 0.27, CH ₃ OH)	C ₁₁ H ₁₁ FN ₂ O ₅ ·0.2H ₂ O	C, H, N
40	190–192 dec (E)	–59.40 (<i>c</i> 0.17, CH ₃ OH)	C ₁₁ H ₁₂ BrFN ₂ O ₅	C, H, N

^a Solvent for either recrystallization or chromatography: A, Et₂O; B, hexanes/EtOAc; C, CH₃OH; D, 95% EtOH/H₂O; E, CH₃OH/CHCl₃; F, EtOH; G, 2-propanol; H, EtOH/hexanes.

The toxicities of these nucleosides have also been assessed in 2.2.15 cells as well as CEM cells. No significant toxicities were found for any of these analogues with concentrations up to 200 μM, which indicated a high selectivity (over 2000, 140, and 40 for compound **13**, **27**, and **35**, respectively).

The results obtained above are consistent with the general observation that L-nucleosides often showed lower toxicity than their D-isomers and most of the active L-nucleosides against HIV and/or HBV are cytosine derivatives.^{1–8} Therefore, L-FMAU may be unique in a sense that this is the only thymine derivative of an L-nucleoside discovered so far with potent anti-HBV activity. Furthermore, L-FMAU is the only 2'-deoxy nucleoside with a 3'-OH group, while all the other identified anti-HBV L-nucleosides lack that OH group. It is well-known that HBV replicates by a multistep mechanism that involves the reverse transcription of a pregenomic RNA;³⁷ therefore, most of the active L-nucleosides such as 3TC, FTC, and L-FddC are 2',3'-dideoxycytidine analogues, which may act as chain terminators.³⁸ The structural uniqueness of L-FMAU may implicate that the mode of action of L-FMAU is different from that of other cytosine derivatives, and therefore, potential cross-resistance problems may be avoided after a prolonged use of these compounds in patients. Although presently the precise mechanism of action of L-FMAU is not clear, preliminary biochemical study suggested that inhibition of viral DNA polymerase may account for its anti-HBV activity.¹⁵

In summary, we have developed an efficient procedure for the preparation of the L-ribose derivative **6** from

L-xylose, which was further used for the synthesis of L-FMAU (**13**) as well as other 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)pyrimidine nucleosides. From the study of comprehensive structure–activity relationships, we discovered that L-FMAU exhibited the most potent anti-HBV activity among these pyrimidine nucleoside analogues with a high selectivity index (>2000). The cytosine (**27**) and 5-iodocytosine (**35**) derivatives also showed moderately potent anti-HBV activity with selectivities of 140 and 40, respectively. The anti-EBV activity study of these new analogues is still ongoing in laboratories. Although further biochemical studies are needed to elucidate the antiviral mechanism of these L-nucleosides, synthesis of additional nucleoside analogues is warranted.

Experimental Section

Melting points were determined on a Mel-temp II and are uncorrected. ¹H NMR spectra were recorded on a JEOL FX 90Q Fourier-transform spectrometer for 90 MHz or on a Bruker 250 AM for 250 MHz, 300 AC for 300 MHz, or 400 AMX spectrometer for 400 MHz, with Me₄Si as internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broad singlet). IR spectra were measured on a Nicolet 510P FT-IR spectrometer. Optical rotations were performed on a JASCO DIP-370 digital polarimeter. TLC were performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either silica gel 60 (220–440 mesh) for flash chromatography or silica gel G (TLC grade >440 mesh) for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU-7 or on a Beckman DU 650 spectrophotometer. Elemental analyses were performed by

Table 2. ^1H NMR Data of Synthesized Nucleosides and Some $\text{C}_1\text{-F}$ Coupling Constants of ^{13}C NMR

no.	H-1'	H-2'	H-3'	H-4'	H-5',5''	$J_{\text{C}_1\text{-F}}$	others	solvent
12	6.35 (dd, $J_{\text{F-H}} = 22.4$)	5.32 (dd, $J_{\text{F-H}} = 50.2$)	5.64 (dd, $J_{\text{F-H}} = 20.4$)	4.50 (m)	4.82 (m)		8.55 (s, NH), 7.37, 8.12 (m, Ar), 1.76, (s, CH_3)	CDCl_3
13	6.10 (dd, $J_{\text{F-H}} = 15.4$)	5.04 (dt, $J_{\text{F-H}} = 52.8$)	4.22 (dq, $J_{\text{F-H}} = 18.4$)	3.76 (m)	3.63 (m)	16.59	11.45 (s, NH), 7.59 (s, H-6), 5.88 (d, 3'-OH), 5.13 (t, 5'-OH), 1.78 (s, CH_3)	DMSO- d_6
14	6.35 (dd, $J_{\text{F-H}} = 22.1$)	5.32 (dd, $J_{\text{F-H}} = 50.3$)	5.65 (dd, $J_{\text{F-H}} = 17.8$)	4.50 (m)	4.83 (m)		8.16 (s, NH), 7.32, 8.11 (m, Ar), 2.21, (q, CH_2CH_3), 0.97 (t, CH_2CH_3)	CDCl_3
15	6.14 (dd, $J_{\text{F-H}} = 14.1$)	5.08 (dt, $J_{\text{F-H}} = 53.2$)	4.24 (dq, $J_{\text{F-H}} = 20.3$)	3.78 (m)	3.64 (m)	17.02	11.43 (s, NH), 7.57 (s, H-6), 5.88 (d, 3'-OH), 5.17 (t, 5'-OH), 2.21 (q, CH_2CH_3), 1.02 (t, CH_2CH_3)	DMSO- d_6
16	6.30 (dd, $J_{\text{F-H}} = 21.2$)	5.33 (dd, $J_{\text{F-H}} = 50.1$)	5.62 (dd, $J_{\text{F-H}} = 17.0$)	4.76 (m)	4.85 (m)		8.23 (s, NH), 7.44, 8.10 (m, Ar)	CDCl_3
17	6.07 (dd, $J_{\text{F-H}} = 14.0$)	5.06 (dt, $J_{\text{F-H}} = 52.8$)	4.22 (dt, $J_{\text{F-H}} = 20.4$)	3.76 (m)	3.62 (m)		11.95 (s, NH), 8.10 (d, H-6, $J = 6.89$), 5.90 (d, 3'-OH), 5.22 (t, 5'-OH)	DMSO- d_6
18	6.30 (dd, $J_{\text{F-H}} = 21.1$)	5.32 (dd, $J_{\text{F-H}} = 50.1$)	5.64 (dd, $J_{\text{F-H}} = 17.3$)	4.54 (m)	4.82 (m)	16.58	8.19 (s, NH), 7.44, 8.10 (m, Ar)	CDCl_3
19	6.10 (dd, $J_{\text{F-H}} = 14.3$)	5.08 (dt, $J_{\text{F-H}} = 52.8$)	4.24 (dt, $J_{\text{F-H}} = 19.9$)	3.82 (m)	3.66 (m)		11.70 (s, NH), 8.13 (s, H-6), 5.87 (d, 3'-OH), 5.20 (t, 5'-OH)	DMSO- d_6
20	6.30 (dd, $J_{\text{F-H}} = 21.1$)	5.32 (dd, $J_{\text{F-H}} = 50.2$)	5.64 (dd, $J_{\text{F-H}} = 17.4$)	4.54 (m)	4.82 (m)		8.14 (s, NH), 7.45, 8.11 (m, Ar)	CDCl_3
21	5.94 (dd, $J_{\text{F-H}} = 14.0$)	4.92 (dt, $J_{\text{F-H}} = 52.8$)	4.09 (dt, $J_{\text{F-H}} = 21.0$)	3.65 (m)	3.48 (m)		11.63 (s, NH), 8.12 (s, H-6), 5.70 (d, 3'-OH), 5.06 (t, 5'-OH)	DMSO- d_6
22	6.29 (dd, $J_{\text{F-H}} = 19.4$)	5.53 (dd, $J_{\text{F-H}} = 50.6$)	5.68 (dd, $J_{\text{F-H}} = 23.6$)	4.60 (m)	4.73 (m)		11.95 (s, NH), 7.50, 8.06 (m, Ar)	CDCl_3
23	6.08 (dd, $J_{\text{F-H}} = 13.7$)	5.07 (dt, $J_{\text{F-H}} = 53.0$)	4.24 (br d, $J_{\text{F-H}} = 21.0$)	3.81 (m)	3.55 (m)	17.03	11.82 (s, NH), 8.24 (s, H-6), 5.95 (d, 3'-OH), 5.30 (t, 5'-OH)	DMSO- d_6
24	6.31 (dd, $J_{\text{F-H}} = 20.7$)	5.37 (dd, $J_{\text{F-H}} = 49.9$)	5.64 (dd, $J_{\text{F-H}} = 14.5$)	4.58 (m)	4.85 (m)		7.43, 8.12 (m, Ar, NH)	CDCl_3
25	6.14 (dd, $J_{\text{F-H}} = 11.0$)	5.16 (dt, $J_{\text{F-H}} = 52.8$)	4.20 (dq, $J_{\text{F-H}} = 20.1$)	3.81 (m)	3.59 (m)		12.05 (br s, NH), 8.51 (s, H-6), 5.94 (d, 3'-OH), 5.34 (t, 5'-OH)	DMSO- d_6
26	6.42 (dd, $J_{\text{F-H}} = 21.0$)	5.57 (dd, $J_{\text{F-H}} = 49.7$)	5.65 (dd, $J_{\text{F-H}} = 16.5$)	4.60 (m)	4.83 (m)		7.44, 8.11 (m, Ar, NH)	CDCl_3
27	6.08 (dd, $J_{\text{F-H}} = 18.4$)	4.92 (dt, $J_{\text{F-H}} = 52.2$)	4.16 (dt, $J_{\text{F-H}} = 18.6$)	3.79 (m)	3.53 (m)		7.61 (d, H-6, $J = 7.4$), 7.21 (br d, NH_2), 5.72 (d, H-5, $J = 7.5$)	DMSO- d_6
28	6.36 (dd, $J_{\text{F-H}} = 21.7$)	5.43 (dd, $J_{\text{F-H}} = 49.8$)	5.60 (dd, $J_{\text{F-H}} = 16.8$)	4.52 (m)	4.80 (m)		7.44, 8.10 (m, Ar, NH_2)	CDCl_3
29	6.03 (dd, $J_{\text{F-H}} = 16.6$)	4.97 (dt, $J_{\text{F-H}} = 49.7$)	4.18 (dt, $J_{\text{F-H}} = 19.4$)	3.78 (m)	3.58 (m)		7.90 (d, H-6, $J = 8$), 7.61, 7.86 (2s, NH_2), 5.82 (d, 3'-OH), 5.11 (t, 5'-OH)	DMSO- d_6
30	6.38 (dd, $J_{\text{F-H}} = 21.4$)	5.44 (dd, $J_{\text{F-H}} = 49.7$)	5.62 (dd, $J_{\text{F-H}} = 16.8$)	4.53 (m)	4.81 (m)		7.44, 8.11 (m, Ar, NH_2)	CDCl_3
31	6.04 (dd, $J_{\text{F-H}} = 16.6$)	4.98 (dt, $J_{\text{F-H}} = 52.4$)	4.18 (dt, $J_{\text{F-H}} = 17.0$)	3.78 (m)	3.58 (m)	16.69	7.96 (s, H-6), 7.33, 7.96 (2s, NH_2), 5.84 (d, 3'-OH), 5.14 (t, 5'-OH)	DMSO- d_6
32	6.38 (dd, $J_{\text{F-H}} = 21.4$)	5.42 (dd, $J_{\text{F-H}} = 49.8$)	5.62 (dd, $J_{\text{F-H}} = 16.8$)	4.52 (m)	4.82 (m)		7.44, 8.11 (m, Ar, NH_2)	CDCl_3
33	6.04 (dd, $J_{\text{F-H}} = 16.6$)	4.98 (dt, $J_{\text{F-H}} = 52.5$)	4.18 (dt, $J_{\text{F-H}} = 20.1$)	3.78 (m)	3.60 (m)		8.02 (s, H-6), 7.12, 7.97 (2s, NH_2), 5.82 (d, 3'-OH), 5.16 (t, 5'-OH)	DMSO- d_6
34	6.41 (dd, $J_{\text{F-H}} = 20.0$)	5.48 (dd, $J_{\text{F-H}} = 50.0$)	5.65 (dd, $J_{\text{F-H}} = 17.5$)	4.58 (m)	4.85 (m)		10.93 (br s, NH), 7.45, 8.20 (m, Ar)	CDCl_3
35	6.05 (dd, $J_{\text{F-H}} = 16.80$)	4.98 (dt, $J_{\text{F-H}} = 52.5$)	4.18 (m)	3.78 (m)	3.60 (m)		8.04 (s, H-6), 6.74, 7.94 (2s, NH_2), 5.84 (d, 3'-OH), 5.17 (t, 5'-OH)	DMSO- d_6
36	6.28 (dd, $J_{\text{F-H}} = 21.1$)	5.32 (dd, $J_{\text{F-H}} = 50.1$)	5.62 (dd, $J_{\text{F-H}} = 17.1$)	4.55 (m)	4.80 (m)		8.19 (s, NH), 7.44, 8.10 (m, Ar), 0.23 (s, SiMe_3)	CDCl_3
37	5.90 (dd, $J_{\text{F-H}} = 14.6$)	4.86 (dt, $J_{\text{F-H}} = 52.7$)	4.04 (dt, $J_{\text{F-H}} = 20.8$)	3.62 (m)	3.43 (m)		11.58 (s, NH), 7.90 (s, H-6), 5.68 (d, 3'-OH), 4.99 (t, 5'-OH), 3.91 (s, CCH)	DMSO- d_6
38	6.14 (dd, $J_{\text{F-H}} = 14.2$)	5.10 (dt, $J_{\text{F-H}} = 52.6$)	4.26 (dt, $J_{\text{F-H}} = 19.8$)	3.84 (m)	3.69 (m)		11.79 (s, NH), 8.35 (s, H-6), 7.41 (d, H_a , $J = 15.9$), 6.90 (d, H_b , $J = 15.8$), 5.81 (d, 3'-OH), 5.25 (t, 5'-OH), 3.69 (s, COOCH_3)	DMSO- d_6
39	6.12 (dd, $J_{\text{F-H}} = 14.0$)	5.08 (dt, $J_{\text{F-H}} = 52.7$)	4.27 (dt, $J_{\text{F-H}} = 19.6$)	3.81 (m)	3.65 (m)		11.80 (s, NH), 8.28 (s, H-6), 7.31 (d, H_a , $J = 15.8$), 6.79 (d, H_b , $J = 15.9$), 5.90 (d, 3'-OH), 5.23 (t, 5'-OH)	DMSO- d_6
40	6.10 (dd, $J_{\text{F-H}} = 14.7$)	5.04 (dt, $J_{\text{F-H}} = 52.6$)	4.23 (dt, $J_{\text{F-H}} = 19.9$)	3.80 (m)	3.63 (m)		11.70 (s, NH), 7.97 (s, H-6), 7.26 (d, H_a , $J = 13.6$), 6.88 (d, H_b , $J = 13.6$), 5.86 (d, 3'-OH), 5.12 (t, 5'-OH)	DMSO- d_6

Atlantic Microlab, Inc., Norcross, GA, or Galbraith Laboratories, Inc., Knoxville, TN. Dry 1,2-dichloroethane (DCE) and acetonitrile were obtained by distillation from CaH.

1,2-O-Isopropylidene- α -L-xylofuranose (2). Compound **2** was prepared from L-xylose in 96% yield by the method reported for the synthesis of the D-isomer:²² ^1H NMR (CDCl_3) δ 5.98 (d, $J = 3.8$ Hz, 1H, H-1), 4.52 (d, $J = 3.6$ Hz, 1H, H-2), 4.31 (br d, 1H, H-3), 4.08 (m, 3H, H-4 and H-5), 1.32 and 1.25 (2s, 6H, 2 CH_3).

5-O-Benzoyl-1,2-O-isopropylidene- α -L-xylofuranose (3). To a stirred solution of **2** (91.5 g, 482 mmol) in pyridine (80 mL) and CH_2Cl_2 (400 mL) at 0 °C was added dropwise BzCl (56 mL, 482 mmol). The mixture was stirred at 0 °C for 1 h and washed successively with dilute HCl and saturated NaHCO_3 and dried (MgSO_4). Evaporation of solvent and recrystallization from Et_2O gave **3** as a white solid (116 g, 82%): ^1H NMR (CDCl_3) δ 7.43, 8.07 (m, 5H, Ar-H), 5.97 (d, 1H, $J = 3.6$ Hz, H-1), 4.80 (q, 1H, H-4), 4.60 (d, 1H, $J = 3.6$ Hz, H-2), 4.40, 4.20 (m, 3H, H-5, H-5', H-3), 3.50 (br s, 1H, D_2O exchangeable, 3-OH), 1.51 and 1.32 (2s, 6H, 2 CH_3).

5-O-Benzoyl-1,2-O-isopropylidene- α -L-erythro-pentofuranos-3-ulose (4). To a stirred solution of **3** (40.0 g, 136 mmol) in CH_2Cl_2 (450 mL) were added pyridinium dichromate (PDC, 30.7 g, 81.6 mmol) and Ac_2O (42.3 mL, 449 mmol), and the mixture was refluxed for 1.5 h. The solvent was evaporated, and EtOAc (50 mL) was added. The mixture was applied to a silica gel pad (10 cm \times 5 cm) and eluted with EtOAc . The combined eluant was concentrated and coevaporated with toluene (2 \times 50 mL). The residue was recrystallized from hexanes- EtOAc to give **4** as a white solid (38.0 g, 96%): IR (KBr) 1773, 1730 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.97, 7.42 (m, 5H, Ar-H), 6.14 (d, 1H, $J = 4.4$ Hz, H-1), 4.74, 4.68 (m, 2H, H-4, H-2), 4.50, 4.44 (m, 2H, H-5, H-5'), 1.52 and 1.44 (2s, 6H, 2 CH_3).

1,2-O-Isopropylidene- α -L-ribofuranose (5a). To a stirred mixture of **4** (37.0 g, 127 mmol) in $\text{EtOH-H}_2\text{O}$ (400:100 mL) at 0 °C was added NaBH_4 (23.3 g, 612 mmol) portionwise, and the suspension was stirred at room temperature for 4 h. It was filtered, and the filtrate was evaporated to dryness and coevaporated with methanol. After silica gel column chroma-

Table 3. Median Effective (EC₅₀) and Inhibitory (IC₅₀) Concentration of 2'-Fluoro-β-L-arabinofuranosyl Pyrimidine Nucleosides in 2.2.15 Cells and Cytotoxicity in CEM Cells

no.	base	EC ₅₀ (μM) anti-HBV activity in 2.2.15 cells	IC ₅₀ (μM)		selectivity 2.2.15-HBV
			2.2.15	CEM	
13	5-methyluracil (T)	0.1	>200	>200	>2000
15	5-ethyluracil	>10	>200	ND ^a	
17	5-fluorouracil	>10	>200	ND	
19	5-chlorouracil	>10	>200	ND	
21	5-bromouracil	>10	>200	ND	
23	5-iodouracil	>10	>200	ND	
25	5-(trifluoromethyl)uracil	>10	>200	ND	
27	cytosine	1.4	>200	>100	>140
29	5-fluorocytosine	>10	>200	ND	
31	5-chlorocytosine	>10	>200	ND	
33	5-bromocytosine	>10	>200	ND	
35	5-iodocytosine	5	>200	ND	>40
37	5-ethynyluracil	>10	>200	ND	
40	5(<i>E</i>)-(bromovinyl)uracil	>10	>200	>100	

^a ND: not determined.

tography (0–15% CH₃OH–CH₂Cl₂) and recrystallization from EtOAc–hexanes, **5a** was obtained as white needles (19.0 g, 79%): IR (KBr) 3356 cm⁻¹; ¹H NMR (CDCl₃) δ 5.83 (d, 1H, *J* = 4.0 Hz, H-1), 4.60 (t, 1H, H-2), 4.06, 3.72 (m, 4H, H-3, H-4, H-5, H-5'), 2.38 (d, 1H, D₂O exchangeable, 3-OH), 1.83 (t, 1H, D₂O exchangeable, 5-OH), 1.58 and 1.38 (2s, 6H, 2 CH₃).

5-O-Benzoyl-1,2-O-isopropylidene-α-L-ribofuranose (5b). To a stirred solution of **4** (14.0 g, 48 mmol) in anhydrous EtOH (60 mL) and EtOAc (30 mL) at 0 °C was added portionwise NaBH₄ (2.2 g, 57 mmol). The mixture was stirred at 0 °C for 1 h and then neutralized with dilute AcOH. Solvent was evaporated, and the residue was redissolved with CH₂Cl₂, washed with water, and dried (MgSO₄). Removal of solvent and recrystallization from EtOAc–hexanes gave **5b** as a white solid (13.8 g, 96.5%): ¹H NMR (CDCl₃) δ 7.40, 8.04 (m, 5H, Ar), 5.86 (d, 1H, *J* = 5.0 Hz, H-1), 4.72 (m, 3H, H-4, H-5), 4.10 (m, 1H, H-2), 4.40 (br s, 1H, D₂O exchangeable, 3-OH), 3.95 (dd, *J* = 4.1, 8.3 Hz, 1H, H-3), 1.60 and 1.38 (2s, 6H, 2 CH₃).

3,5-Di-O-Benzoyl-1,2-O-isopropylidene-α-L-ribofuranose (6). To a stirred solution of **5a** (19.0 g, 100 mmol) in pyridine (300 mL) at 0 °C was added dropwise BzCl (40 mL, 348 mmol), and the mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was extracted with EtOAc, washed with saturated NaHCO₃, and dried (Na₂SO₄). Removal of solvent and recrystallization of the residue from ether gave **7** as a white solid (39.0 g, 98%): ¹H NMR (CDCl₃) δ 8.07, 7.36 (m, 10H, Ar-H), 5.94 (d, 1H, *J* = 3.6 Hz, H-1), 5.05, 5.00 (m, 1H, H-2), 4.73, 4.63 (m, 3H, H-4, H-5, H-5'), 1.58 and 1.35 (2s, 6H, 2 CH₃).

1-O-Acetyl-2,3,5-tri-O-benzoyl-β-L-ribofuranose (7). **Method A.** Compound **7** was prepared from L-ribose in 54% total yield according to a procedure for the synthesis of the D-isomer.³⁹

Method B. A suspension of **6** (38.0 g, 95 mmol) in 1% HCl/CH₃OH (300 mL) was stirred at room temperature until a clear solution was obtained (30 h). Pyridine (20 mL) was added and then evaporated to dryness. The residue was coevaporated with pyridine (2 × 30 mL) and then redissolved in 100 mL of anhydrous pyridine at 0 °C. To this solution was added dropwise BzCl (17.0 mL, 146 mmol), and the mixture was stirred at room temperature for 3 h. It was evaporated to dryness and then extracted with EtOAc. The combined extracts were washed successively with dilute HCl solution and saturated NaHCO₃ and dried (Na₂SO₄). Removal of the solvent gave a syrup that was stirred in a mixture of glacial acetic acid (400 mL) and Ac₂O (100 mL) at 0 °C. To this solution was added dropwise concentrated H₂SO₄ (10 mL), and then the mixture was stirred at room temperature overnight. The mixture was poured into ice–water and extracted with CHCl₃ (4 × 100 mL). The combined extract was washed with saturated NaHCO₃ and dried (Na₂SO₄). Removal of solvent and recrystallization of the residue from methanol gave **7** as a white solid (23.9 g, 49.6%): mp 124–125 °C (lit.¹⁸ mp 129–130 °C); [α]_D –45.6 (c 1.0, CHCl₃) [lit.¹⁸ [α]_D –43.6 (c 1.0, CHCl₃); ¹H NMR (CDCl₃) δ 7.32, 8.13 (m, 15H, Ar-H), 6.44

(s, 1H, H-1), 5.84 (m, 2H, H-2 and H-3), 4.65 (m, 3H, H-4 and H-5), 2.00 (s, 3H, CH₃COO).

1,3,5-Tri-O-benzoyl-α-L-ribofuranose (8). HCl(g) was bubbled through a solution of **7** (23.9 g, 47.4 mmol) in anhydrous CH₂Cl₂ (220 mL) and AcCl (3.6 mL) at 0 °C for 1.5 h. The resulting solution was kept in a refrigerator for 12 h and then evaporated *in vacuo*, and the residue was coevaporated with toluene (3 × 70 mL) and redissolved in CH₃CN (50 mL). To this stirred solution was added dropwise water (6 mL). The white precipitate obtained was dissolved in CHCl₃, washed with saturated NaHCO₃, and dried (MgSO₄). Removal of solvent and coevaporation with Et₂O gave a white solid (15.5 g, 71.0%): ¹H NMR (CDCl₃) δ 7.31, 8.19 (m, 15H, Ar-H), 6.69 (d, *J* = 4.6 Hz, H-1), 5.59 (dd, *J* = 6.7, 1.8 Hz, 1H, H-3), 4.64, 4.80 (m, 4H, H-2, H-4 and H-5), 2.30 (br s, D₂O exchangeable, OH).

1,3,5-Tri-O-benzoyl-2-O-(imidazolylsulfonyl)-α-L-ribofuranose (9). To a stirred solution of **8** (15.0 g, 32.4 mmol) in anhydrous CH₂Cl₂ (150 mL) and DMF (40 mL) at –40 °C was added sulfuryl chloride (10.6 mL, 91.0 mmol) through a syringe. The resulting solution was stirred at –40 °C for 30 min and then gradually warmed up to room temperature. After 3 h, imidazole (32.0 g, 469 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 15 h. The hazy solution was diluted with CH₂Cl₂ (300 mL) and washed with ice–water (400 mL), and the aqueous layer was extracted again with CH₂Cl₂ (3 × 75 mL). The combined organic layer was dried (MgSO₄). Removal of solvent and purification by silica gel column chromatography (5:1–1:1 hexanes–EtOAc) gave **9** as a white solid (14.0 g, 73.0%): ¹H NMR (CDCl₃) δ 7.00, 8.10 (m, 18H, Ar-H), 6.72 (d, *J* = 4.4 Hz, 1H, H-1), 5.60 (dd, *J* = 6.5, 2.9 Hz, 1H, H-3), 5.26 (dd, *J* = 4.5, 6.2 Hz, 1H, H-2), 4.58, 4.80 (m, 3H, H-4 and H-5).

1,3,5-Tri-O-benzoyl-2-deoxy-2-fluoro-α-L-arabinofuranose (10). A suspension of **9** (14.0 g, 23.6 mmol) and KHF₂ (7.4 g, 94.4 mmol) in 2,3-butanediol (120 mL) was stirred under N₂ at 160 °C. To this was added HF–H₂O (48%, 3.4 mL, 94.4 mmol), and the mixture was stirred at 160 °C for 1 h. It was quenched by brine–ice and then extracted with CH₂Cl₂ (4 × 50 mL). The combined extract was washed successively with brine, water, and saturated NaHCO₃ and dried (MgSO₄ and activated charcoal). It was applied on a silica gel pad (5 cm × 5 cm), eluted with CH₂Cl₂ to give a syrup which was recrystallized from 95% EtOH to give **10** (7.1 g, 65%): ¹H NMR (CDCl₃) δ 7.38, 8.11 (m, 15H, Ar-H), 6.76 (d, *J* = 9.2 Hz, 1H, H-1), 5.39 (d, *J*_{F–H} = 48.3 Hz, 1H, H-2), 5.63 (dd, *J* = 2.9, 16.6 Hz, 1H, H-3), 4.65, 4.81 (m, 3H, H-4 and H-5).

1-(3,5-Di-O-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)thymine (12). **General Procedure for Coupling.** To a solution of **10** (2.78 g, 6.0 mmol) in anhydrous CH₂Cl₂ (20 mL) was added HBr–AcOH (45% v/v, 4.6 mL, 25 mmol), and the solution was stirred at room temperature for 20 h. The mixture was evaporated to dryness, dissolved in CH₂Cl₂ (50 mL), and washed with saturated NaHCO₃ (3 × 30 mL). Removal of solvent gave **11** as a syrup (2.55 g, 100%) that was

used without further purification. At the same time, thymine (1.9 g, 15 mmol) and $(\text{NH}_4)_2\text{SO}_4$ (0.1 g) were stirred in refluxing HMDS (30 mL) under nitrogen for 17 h, and the homogeneous solution obtained was evaporated under vacuum to give the silylated thymine.

A solution of **11** in dichloroethane (DCE, 25 mL) was added to the silylated thymine, and the mixture was refluxed under N_2 for 15 h. It was quenched with ice-water, extracted with CH_2Cl_2 (3×45 mL), washed with saturated NaHCO_3 (3×50 mL) and brine, and dried (MgSO_4). Removal of solvent gave a white solid which was purified on silica gel column (1% $\text{MeOH}-\text{CHCl}_3$) to give **12** (2.0 g, 71%): UV (MeOH) λ_{max} 264.0 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)thymine (13, L-FMAU). A solution of **12** (1.70 g, 3.60 mmol) in saturated $\text{NH}_3-\text{CH}_3\text{OH}$ (30 mL) was stirred at room temperature for 15 h and then evaporated to dryness. The residue was purified by silica gel column chromatography (15:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$) to give **13** (0.75 g, 80%): UV(H_2O) λ_{max} 265.0 (ϵ 9695) (pH 2), 265.5 (ϵ 9647) (pH 7), 265.5 nm (ϵ 7153) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-ethyluracil (14). A mixture of **11** (prepared from **10**, 0.50 g, 1.1 mmol) and silylated 5-ethyluracil (0.75 g, 5.4 mmol) in DCE (10 mL) was refluxed for 20 h under N_2 . After workup and silica gel column chromatography (0–1% $\text{CH}_3\text{OH}-\text{CHCl}_3$), **14** was obtained as a white solid (0.557 g, 100%): UV(CH_3OH) λ_{max} 263.5 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-ethyluracil (15). Compound **14** (0.50 g, 1.0 mmol) was treated with saturated $\text{NH}_3-\text{CH}_3\text{OH}$ (50 mL) as described for **12**. After silica gel column chromatography (0–5% $\text{CH}_3\text{OH}-\text{CHCl}_3$), **15** was obtained as a white solid (0.240 g, 84%): UV(H_2O) λ_{max} 265.0 (ϵ 8350) (pH 2), 265.5 (ϵ 8600) (pH 7), 265.5 nm (ϵ 10 100) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-fluorouracil (16). A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated 5-fluorouracil (0.330 g, 5.4 mmol) in DCE (15 mL) was refluxed for 48 h under N_2 . After workup and silica gel column chromatography (50:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$), **16** was obtained as a white solid (0.400 g, 85%): UV(EtOH) λ_{max} 266.5 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-fluorouracil (17). Compound **16** (0.330 g, 0.7 mmol) was treated with saturated $\text{NH}_3-\text{CH}_3\text{OH}$ (50 mL) as described for **12**. After silica gel column chromatography (15:1–10:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$), **17** was obtained as a white solid (0.130 g, 71%): UV(H_2O) λ_{max} 266.5 (ϵ 10 497) (pH 2), 267.5 (ϵ 9874) (pH 7), 266.5 nm (ϵ 8702) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-chlorouracil (18). A mixture of **11** (prepared from **10**, 0.370 g, 0.8 mmol) and silylated 5-chlorouracil (0.293 g, 2.0 mmol) in DCE (15 mL) was refluxed for 24 h under N_2 . After workup and silica gel column chromatography (50:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$), **18** was obtained as a white solid (0.200 g, 51%): UV(MeOH) λ_{max} 273.5 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-chlorouracil (19). Compound **18** (0.100 g, 0.2 mmol) was treated with saturated $\text{NH}_3-\text{CH}_3\text{OH}$ as described for **12**. After purification by preparative TLC (9:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$) and recrystallization in EtOH , **19** was obtained as a white solid (0.046 g, 80%): UV(H_2O) λ_{max} 274.0 (ϵ 9544) (pH 2), 275.5 (ϵ 9620) (pH 7), 274.0 nm (ϵ 7690) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-bromouracil (20). A mixture of **11** (prepared from **10**, 0.370 g, 0.8 mmol) and silylated 5-bromouracil (0.380 g, 2.0 mmol) in DCE (15 mL) was refluxed for 48 h under N_2 . After workup and recrystallization from $\text{CHCl}_3-\text{CH}_3\text{OH}$, **20** was obtained as a white crystal (0.220 g, 52%): UV(MeOH) λ_{max} 274.5 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-bromouracil (21). Compound **20** (0.187 g, 0.35 mmol) was treated with saturated $\text{NH}_3-\text{CH}_3\text{OH}$ as described for **12**. After purification by preparative TLC (10:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$), **21** was obtained as a white solid (0.087 g, 76%): UV (H_2O) λ_{max} 277.5 (ϵ 6549) (pH 2), 277.0 (ϵ 5826) (pH 7), 275.5 nm (ϵ 4880) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-iodouracil (22). A mixture of **11** (prepared from **10**, 0.390 g, 0.85 mmol) and silylated 5-iodouracil (0.400 g, 1.7 mmol) in DCE (10 mL) was refluxed for 36 h under N_2 . After workup, a yellow solid (0.350 g, 71%) was obtained which was recrystallized from 2-propanol to give **22** as a white solid (0.270 g, 55%): UV (methanol) λ_{max} 276.0 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-iodouracil (23). Compound **22** (0.210 g, 0.36 mmol) was treated with saturated NH_3-MeOH as described for **12**. After purification by preparative TLC (15:1 $\text{CHCl}_3-\text{MeOH}$), **23** was obtained as a white solid (0.120 g, 89%): UV(H_2O) λ_{max} 285.5 (ϵ 7643) (pH 2), 291.5 (ϵ 8261) (pH 7), 277.0 nm (ϵ 5512) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-(trifluoromethyl)uracil (24). A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated 5-(trifluoromethyl)uracil (0.360 g, 2.0 mmol) in DCE (15 mL) was refluxed for 20 h under N_2 . After workup and silica gel column chromatography (50:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$), **24** was obtained as a white solid (0.254 g, 49%): UV (EtOH) 255.5 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-(trifluoromethyl)uracil (25). Compound **24** (0.210 g, 0.4 mmol) was treated with saturated $\text{NH}_3-\text{CH}_3\text{OH}$ as described for **12**. After purification by preparative TLC (15:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$), **25** was obtained as a white powder (0.083 g, 66%): UV(H_2O) λ_{max} 260.0 (ϵ 11 630) (pH 2), 260.0 (ϵ 10 244) (pH 7), 258.5 nm (ϵ 7953) (pH 11).

***N*⁴-Benzoyl-1-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)cytosine (26).** A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated *N*⁴-benzoylcytosine (0.540 g, 2.5 mmol) in CH_3CN (10 mL) was refluxed for 12 h under N_2 . After workup and purification by preparative TLC (100:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$), **26** was obtained (0.160 g, 29%): UV (EtOH) λ_{max} 261.5, 302.0 nm.

1-(2-deoxy-2-fluoro- β -L-arabinofuranosyl)cytosine (27). Compound **26** (0.150 g, 0.27 mmol) was treated with saturated NH_3/MeOH as described for **12**. After purification by preparative TLC (9:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$), **27** was obtained as a white powder (0.060 g, 91%): UV(H_2O) λ_{max} 277.0 (ϵ 12 338) (pH 2), 269.5 (ϵ 7900) (pH 7), 270.0 nm (ϵ 9185) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-fluorocytosine (28). A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated 5-fluorocytosine (0.320 g, 2.5 mmol) in DCE (20 mL) was refluxed for 24 h under N_2 . After silica gel column chromatography (20:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$), **28** was obtained as a white foam (0.180 g, 38.5%): UV(EtOH) λ_{max} 277.0 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-fluorocytosine (29). Compound **28** (0.140 g, 0.3 mmol) was treated with saturated $\text{NH}_3-\text{CH}_3\text{OH}$ as described for **12**. After trituration in acetone followed by recrystallization from EtOH , **29** was obtained as a white solid (0.078 g, 100%): UV(H_2O) λ_{max} 284.0 (ϵ 11 145) (pH 2), 279.5 (ϵ 8138) (pH 7), 279.0 nm (ϵ 9000) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-chlorocytosine (30). A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated 5-chlorocytosine (0.440 g, 3.0 mmol) in DCE (30 mL) was refluxed for 24 h under N_2 . After silica gel column chromatography (20:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$), **30** was obtained as a white foam (0.385 g, 80%): UV (EtOH) λ_{max} 282.5 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-chlorocytosine (31). Compound **30** (0.315 g, 0.65 mmol) was treated with saturated $\text{NH}_3-\text{CH}_3\text{OH}$ as described for **12**. After trituration in acetone followed by recrystallization from EtOH , **31** was obtained as a white powder (0.106 g, 59%): UV(H_2O) λ_{max} 291.0 (ϵ 11 226) (pH 2), λ_{max} 285.0 (ϵ 8813) (pH 7), 284.5 nm (ϵ 9859) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-bromocytosine (32). A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated 5-bromocytosine (0.475 g, 2.5 mmol) in DCE (30 mL) was refluxed for 24 h under N_2 . After silica gel column chromatography (20:1 $\text{CHCl}_3-\text{CH}_3\text{OH}$), **32** was obtained as a white foam (0.350 g, 66%): UV (EtOH) λ_{max} 285.0 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-bromocytosine (33). Compound **32** (0.290 g, 0.55 mmol) was treated with saturated $\text{NH}_3\text{-CH}_3\text{OH}$ as described for **12**. After trituration in acetone followed by recrystallization from EtOH, **33** was obtained as a white solid (0.088 g, 50%): UV(H_2O) λ_{max} 294.0 (ϵ 9284) (pH 2), 286.5 (ϵ 6757) (pH 7), 286.5 nm (ϵ 7721) (pH 11).

N³-Benzoyl-1-(3,5-di-O-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-iodocytosine (34). A mixture of **11** (prepared from **10**, 0.150 g, 0.32 mmol) and silylated N³-benzoyl-5-iodocytosine (0.550 g, 1.6 mmol) in DCE (10 mL) was refluxed for 24 h under N_2 . After workup and silica gel column chromatography (0–1% $\text{CH}_3\text{OH-CHCl}_3$), **34** was obtained as a white solid (0.100 g, 45%): UV (CH_3OH) λ_{max} 345.0, 316.0 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-iodocytosine (35). Compound **34** (0.100 g, 0.27 mmol) was treated with saturated $\text{NH}_3\text{-MeOH}$ as described for **12**. After silica gel column chromatography (0–10% $\text{CH}_3\text{OH-CHCl}_3$), **35** was obtained as a white solid (0.035 g, 71%): UV(H_2O) λ_{max} 306.0 (ϵ 8300) (pH 2), 292.0 (ϵ 5710) (pH 7), 292.0 nm (ϵ 5400) (pH 11).

1-(3,5-Di-O-benzoyl-2-deoxy-2-fluoro- β -L-arabinofuranosyl)-5-[2-(trimethylsilyl)acetylenyl]uracil (36). Argon was purged through Et_3N (60 mL) for 0.5 h. To this was added **22** (0.580 g, 1.0 mmol), followed by (trimethylsilyl)acetylene (0.283 mL, 2.0 mmol), CuI (30 mg), and $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (30 mg). The mixture was stirred at 50–60 °C for 4.5 h and then evaporated to dryness. The residue was dissolved in CHCl_3 (100 mL), washed with 5% EDTA solution (3 \times 50 mL) and saturated NaHCO_3 , and dried (MgSO_4). After removal of the solvent, followed by purification on a silica gel column (50:1 $\text{CHCl}_3\text{-CH}_3\text{OH}$) and recrystallization from $\text{CHCl}_3\text{-CH}_3\text{OH}$, **36** was obtained as a white powder (0.400 g, 73%): UV (EtOH) λ_{max} 241.0, 284.5 nm.

1-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-ethynyluracil (37). Compound **36** (0.350 g, 0.64 mmol) was stirred in 0.2 N $\text{NaOCH}_3\text{-CH}_3\text{OH}$ (15 mL) at room temperature for 4 h. It was neutralized with Dowex 50W \times 8 (H^+) resin, then filtered, and washed with methanol. The combined filtrate was evaporated to dryness. Column separation (9:1 $\text{CHCl}_3\text{-CH}_3\text{OH}$) and recrystallization from EtOH–hexanes gave **37** as a white solid (0.140 g, 82%): UV(H_2O) λ_{max} 284.5 (ϵ 8932) (pH 2), 284.5 (ϵ 10 383) (pH 7), 281.5 nm (ϵ 9556) (pH 11).

(E)-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-[2-(methoxycarbonyl)vinyl]uracil (38). A mixture of Ph_3P (0.040 g, 0.15 mmol), $\text{Pd}(\text{OAc})_2$ (0.020 g, 0.08 mmol), and Et_3N (0.4 mL, 2.8 mmol) in 1,4-dioxane (15 mL) was refluxed to form a dark-red solution and then cooled to just below reflux. To this was added methyl acrylate (0.36 mL, 4.0 mmol), followed by **23** (0.300 g, 0.8 mmol) with dioxane (10 mL) and Et_3N (0.15 mL). The mixture was refluxed for 0.5 h, filtered through a Celite pad, and washed with dioxane. The combined filtrate was evaporated to dryness and purified on a silica gel column (9:1 $\text{CHCl}_3\text{-CH}_3\text{OH}$) to give **38** as a white foam (0.145 g, 54%): UV(MeOH) λ_{max} 299.0 nm; $^1\text{H NMR}$ ($\text{DMSO-}d_6$) δ 11.79 (s, 1H, D_2O exchangeable, CONH), 8.35 (s, 1H, H-6), 7.41 (d, 1H, $J = 15.9$ Hz, Ha), 6.90 (d, 1H, $J = 15.8$ Hz, Hb), 6.14 (dd, $J_{\text{F-H}} = 14.2$ Hz, H-1'), 5.81 (d, 1H, D_2O exchange 3'-OH), 5.25 (t, 1H, D_2O exchangeable, 5'-OH), 5.10 (dt, $J_{\text{F-H}} = 52.6$ Hz, 1H, H-2'), 4.26 (dt, $J_{\text{F-H}} = 19.8$ Hz, 1H, H-3'), 3.84 (m, 1H, H-4'), 3.69 (dm, 2H, H-5'a,b). Anal. ($\text{C}_{12}\text{H}_{15}\text{F N}_2\text{O}_7\cdot 0.8\text{H}_2\text{O}$) C, H, N.

(E)-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-(2-carboxyvinyl)uracil (39). A solution of **38** (0.135 g, 0.41 mmol) in a 2 N NaOH solution (5 mL) was stirred at room temperature for 1.5 h and then cooled in an ice bath. It was carefully adjusted to ca. pH 1 with 12 N HCl and stirred for 10 min. The white precipitate was collected by filtration and washed with water and acetone to give **39** as a white powder (0.096 g, 74%): mp 284 °C dec; UV(MeOH) λ_{max} 298.0, 268.0 nm (shoulder); $^1\text{H NMR}$ ($\text{DMSO-}d_6$) δ 11.80 (s, 1H, D_2O exchangeable, CONH), 8.28 (s, 1H, H-6), 7.31 (d, 1H, $J = 15.8$ Hz, Ha), 6.79 (d, 1H, $J = 15.9$ Hz, Hb), 6.12 (dd, $J_{\text{F-H}} = 14.0$ Hz, H-1'), 5.90 (d, 1H, D_2O exchangeable 3'-OH), 5.23 (t, 1H, D_2O exchangeable, 5'-OH), 5.08 (dt, $J_{\text{F-H}} = 52.7$ Hz, 1H, H-2'), 4.27

(dt, $J_{\text{F-H}} = 19.6$ Hz, 1H, H-3'), 3.81 (m, 1H, H-4'), 3.65 (dm, 2H, H-5'a,b). Anal. ($\text{C}_{12}\text{H}_{13}\text{FN}_2\text{O}_7\cdot 1.6\text{H}_2\text{O}$) C, H, N.

(E)-(2-Deoxy-2-fluoro- β -L-arabinofuranosyl)-5-(2-bromovinyl)uracil (40). A suspension of **39** (0.080 g, 0.25 mmol) and KHCO_3 (0.100 g, 1.0 mmol) in DMF (1.5 mL) was stirred at room temperature for 20 min. To this was added *N*-bromosuccinimide (0.053 g, 0.3 mmol) in DMF (1.0 mL). The mixture was stirred at room temperature for 1.5 h, filtered, and washed with methanol. The filtrate was evaporated to dryness and purified on PTLC (6:1 $\text{CHCl}_3\text{-CH}_3\text{OH}$). After coevaporation with ether, **40** was obtained as a white foam (0.047 g, 53%): UV(H_2O) λ_{max} 250.0 (ϵ 15 844) (pH 2), 250.0 (ϵ 14 622) (pH 7), 254.0 nm (ϵ 15 912) (pH 11).

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Supporting Information Available: X-ray data for L-FMAU (35 pages). Ordering information is given on any current masthead page.

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